REMARKS

Claims 1-20 were pending in the application. By this response, applicant has amended claims 2-9, 11-20; canceled claims 1 and 10; and added new claims 21 to 41. As such, claims 2-9 and 11-41 are presented for the Examiner's consideration in the light of the following remarks. Reconsideration of the merits of the application is respectfully requested.

Proposed Claim Amendments

Claims 2-9 and 11-20 have been amended to render them dependent from new independent claims introduced in this response. New claims 21-41 have been introduced to address the formal objections as set forth within the official action. New claims 21-41 are supported by the specification as originally filed.

In particular, new claim 21 is supported by old claim 1 and page 3 of the specification as originally filed; new claims 22 and 23 supported by page 4 of the specification as originally filed; new claims 24 and 25 are supported by page 10 of the specification as originally filed; new claims 26 and 27 are supported by page 4 of the specification as originally filed; new claim 28 is supported by page 3 of the specification as originally filed; new claims 29 to 32 have equivalent support to new claims 22 to 25; new claim 33 is supported by claim 1 and page 5 of the specification as originally filed; new claims 34-40 are supported by pages 5 and 13 to 14 of the specification as originally filed; new claim 41 is supported by original claim 1 and page 4 of the specification as originally filed.

In view of the foregoing, the applicant respectfully submits that the claim amendments do not introduce new matter, an entry thereof is respectfully requested.

Priority

Paragraph 1 of the official action noted the non-filing of a certified copy of the British application as required by 35USC§119(b). A certified copy of the British application has been requested and will be forwarded to the US Patent and Trademark Office shortly.

Information Disclosure Statement

Paragraph 2 of the official action indicated that a copy of each reference is required before the IDS will be considered. A copy of each reference will be supplied shortly.

Anticipation and Obviousness Rejections

Paragraph 4 of the official action rejected claims 1-7, 11-14 and 16-20 under 35USC§102(b) as being anticipated by Weir et al. The applicant respectfully traverses this rejection.

Paragraph 6 of the official action rejects claims 1-8, 11-14 and 16-20 under 35USC§103(a) as being unpatentable over Weir et al in view of US 5593832 to Glassberg. The applicant respectfully traverses this rejection.

Paragraph 7 of the official action rejected claims 1-7, 9-14 and 16-20 under 35USC§103(a) as being unpatentable over Weir et al in view of Jarjoura et al. The applicant respectfully traverses this rejection.

Paragraph 8 of the official action rejected claims 1-7 and 11-20 as being unpatentable over Weir et al in view of US 5702885 to Baxter-Lowe. The applicant respectfully traverses this rejection.

The rejections set forth in paragraphs 4, 6, 7, and 8 of the official action will be addressed together. The present claims are not anticipated by the Weir et al reference. None of the other references cited by the Examiner overcome the deficiencies in Weir to make the presently claimed invention obvious.

Claims 21-32

Independent claims 21 and 28 and their respective dependent claims, claims 22 to 27 and claims 29 to 32 are distinguished from the prior art of record in that they provide the feature that the

minimum number of loci needed to achieve a minimum combined likelihood ratio is calculated from:

$$\overline{LRn} = \prod_{m=1}^{mp} LR^{(fmxn)}$$

in the case of claim 21, and in relation to claim 28 because that claim relates to

a method of estimating the minimum number of loci to be used

and in as much as that estimate achieves its aim by the case of

the theoretical likelihood ratio calculated from

$$\overline{LRn} = \prod_{m=1}^{mp} LR^{(fmxn)}$$

There is no suggestion within Weir et al or within the other prior art of record that the minimum number of loci needed in a multiplex can be calculated in this way.

Weir is concerned with an old technique, RFLP (see page 213, right column, third paragraph, line 3 and elsewhere). RFLP is concerned with the analysis of the identity of variations which occur at certain loci. The variation takes on one of a substantial number of identities at each loci; in contrast to the present invention where one of only two possibilities is possible at each loci. The hypervariability possessed by RFLP based analysis, as exemplified by Weir, means that only a small number of loci need to be considered to give a meaningful power to distinguish between individuals. Each loci could have one or 20-30 different identities. In the case of single nucleotide polymorphisms, however, there are only two possible identities at each loci. To give sufficient distinguishing power, therefore, a far larger number of loci need to be considered, perhaps 100 or more. Consideration of too many loci, however, is wasteful

in terms of time and reagents and can also be problematical where the sample is too small to allow it to be split into so many different tests.

The presently claimed invention addressed this problem through claims 21 and 28 by providing a technique which uses, and a technique which establishes, the minimum number of loci which are need to be investigated to achieve a minimum likelihood value, and hence a power of discrimination. Details of this are discussed at page 10, first paragraph of the application as filed. This is a significant feature as it allows the necessary distinguishing power to be obtained whilst keeping the number of loci down as far as possible.

There is no mention whatsoever of this concept within Weir et al. Indeed, in the context of RFLP base investigations, such a problem does not exist, and no thought would be given to such an issue, therefore. Other problems with RFLP technology do exist, however, and single nucleotide polymorphism based analysis addresses those. In doing so, however, it introduces the issue of how many loci are needed and the present invention is the first to address this issue. As such the inventions claimed in claims 21 and 28 represent a significant contribution to the art by establishing appropriate, thorough and yet cost effective single nucleotide polymorphism based analysis techniques.

Claims 2-9, 11-14, and 33-40

Independent claim 33 and dependent claims 34 to 40 and 2 to 9 and 11 to 14 are distinguished over the prior art in that the prior art does not provide in the case of Weir et al

a determination of the identity of the single nucleotide polymorphism alleles present at a locus

as Weir is concerned with RFLP based analysis which is entirely different to single nucleotide polymorphisms. Furthermore, Weir et al does not provide such a determination for

a plurality of singe nucleotide polymorphism loci

as again Weir is not concerned with SNP loci in any way, shape or form, and most importantly does not provide for

the method including the establishment of a probability value that a person's allele identity or identities have not been detected which reflects the probability that the identity or identities is present but is not distinguished from the background noise.

An issue with RFLP based techniques, such as Weir, is that the hypervariability of the identities of the loci can give rise to alleles which are potentially of very different sizes. This is a substantial problem in the case of very small allele identities as these have resultant very high mobility in the gels which are used to analyses the alleles present. Those alleles tend to migrate all the way through and go off the gel during analysis due to too fast a migration. This leads to the null allele problem discussed at page 217 and elsewhere in Weir. However, the null allele type at issue there is quite different from that in the present invention. In Weir both allele identities are present and are at detectable levels, but one or more is not detected due to that allele no longer being present on the gel. Whilst a large level of the allele is present in the sample, therefore, it is not detected in the gel. That could be corrected by applying a different migration time, but then the large alleles might not be detected.

The presently claimed invention is concerned with being able to account for the possibility that the allele is present, features in the results that are measured, but is indistinguishable from the background noise of the analysis technique. Thus the allele identities are all present on the gel at the end of migration, for instance, but whilst the allele(s) from the major contributor to the mixture is present in an easily detectable

amount the allele(s) from the minor contributor (usually the perpetrator of the crime) may only be present in an amount which is insufficient to give a signal distinguishable from the background.

In prior art techniques this problem represented a limit on the application of such technology and meant it could not be used on samples with a low level of contribution from one party. In cases where this issue arose, no meaningful evaluation was deemed possible. The present invention realises that meaningful information can be gained in such cases by incorporating within the probability value an account for such an occurrence. Furthermore, as set out in the details of claims 34 through 37 precise accounting for these possibilities can be achieved. Nothing within Weir points towards addressing this issue nor the manner in which the present invention addresses it.

With regard to independent claim 41, and dependent 15 to 20 therefrom, once again this is fully distinguished over the prior art of record. With regard to Weir in particular, independent claim 41 is distinguished in as much as it involves

> **a predetermination of the identity of the single nucleotide polymorphism alleles present at a locus**

whereas Weir is concerned with RFLP variations. The use of

> **such likelihood ratios for a plurality of single nucleotide polymorphism loci**

again because Weir uses RFLP based analysis, and most importantly the fact that the method of indicating the likelihood uses

> **loci at which the given person and the known first person are known to have the same homozygous having an identity and which provides the establishment of a probability value that a person's allele identity or**

identities have not been detected, which reflects the probability that the identity or identities is absent, rather than present but not detected.

Within the prior art loci for which homozygous suspects and victims were considered were deemed to be of no use. However, in the present invention it is realised that such a situation can still give useful information to the indication of the likelihood where the determination establishes that the homozygous result arises due to only one allele identity being present (truly homozygous) rather than potentially due to two being present (heterozygous) but one not being detected at a measurable level when compared with the background noise.

Again this provides a significant advance over the prior art in allowing useful information to be obtained from loci which were not previously deemed informative. Again there is no suggestion within the prior art, particularly Weir et al, as to this issue. Weir et al does not suggest accounting in the probability factor for such a case.

Conclusion

In view of the foregoing, the applicant respectfully requests the Examiner's reconsideration and allowance of claims 2-9 and 11-41 as amended as presented herein.

In the event there remains any impediment to allowance of the claims which could be clarified by telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Dated this 14th day of June 2002

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

~~1. (Deleted) A method for indicating the likelihood that a DNA mixture arose from sources of a defined type where the DNA mixture is formed by DNA samples from more than one source, the method involving:~~

~~the determination of the identity of the alleles present at a locus for the DNA in the mixture;~~

~~determining a first probability function for the situation where the DNA mixture is formed from samples arising from the given person and from a first other person;~~

~~determining a second probability function for the situation where the DNA mixture is formed from samples arising from a second other person and a first other person;~~

~~using the first probability function as numerator and the second probability function as denominator in determining a likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;~~

~~determining such likelihood ratios for a plurality of loci; and~~

~~combining the likelihood ratios to give a combined likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function.~~

2. (Amended) A method according to claim 33 [1] in which the first probability function is the probability that the defined type provides one or both of the mixture sources based on the frequency of occurrence of the possible allele combinations which could generate the identified allele identity or identities for that locus.

3. (Amended) A method according to claim 33 [1] in which the second probability function is the probability that the first and second other persons provide the identity for the mixture sources based on the frequency of occurrence of possible allele combinations which could have generated the identified allele identity of identities for that locus.

4. (Amended) A method according to claim 33 [1] where the defined type is the given person and an unknown person, the first function is based on the frequency of

occurrence of the different possible allele combinations for the unknown person which are possible knowing the given persons alleles at that locus.

5. (Amended) A method according to claim 33 [1] where the defined type is the given person and an unknown person, the second function is based on the frequency of occurrence of the different allele combinations which are possible from the two unknown persons which give the allele identity or identities obtained.

6. (Amended) A method according to claim 33 [1] where the defined type is the given person and the first other person is a known person, the first function is defined as 1.

7. (Amended) A method according to claim 33 [1] where the defined type is the given person and the first other person is a known person, the second function is based on the frequency of occurrence of the different possible allele combinations for the unknown person which are possible knowing the known person's alleles at that locus.

8. (Amended) A method according to claim 33 [1] in which the method is applied to at least 20 loci.

9. (Amended) A method according to claim 33 [1] in which the combined likelihood ratio is obtained by multiplying the individual likelihood ratios together.

~~10. A method according to claim 1 in which to estimate the optimum number of loci used in a theoretical likelihood ratio is used, calculated from:-~~

~~$$\frac{}{LRn} = \prod_{m=1}^{mp} LR^{(fmxn)}$$~~

~~where n is the number of loci; mp is the number of possible allele identities for a simple mixture; LR is the likelihood ratio; LR is the combined likelihood ratio; and fm is the proportion of an array of a loci having a particular mixture type m.~~

11. (Amended) A method according to claim 33 [1] where the allele identity or identities of a given person and/or known first other person are under consideration, the method includes the determination of the allele identity or identities at one or more of the loci under consideration from DNA obtained only from the given person or known first person.

12. (Amended) A method according to claim 33 [1] where the defined type is the given person and the first other person is a known person, such as a victim, and at least some of the loci considered in the method are those in which the given person and first other person are known to differ in allele identity.

13. (Amended) A method according to claim 33 [1] where the defined type is the given person and the first other person is a known person, such as a victim, the method considers loci at which the given person and known first person are known to have the same homozygous allele identity.

14. (Amended) A method according to claim 33 [13] in which in such cases the method includes the establishment of a probability value that the other identity is absent.

15. (Amended) A method according to claim 41 [13] in which the probability value involves an investigation of the background noise level from the allele identity investigating process and / or the introduction of one or more negative control samples and / or the determination of a cumulative probability density function for one or more or all of the negative controls.

16. (Amended) A method according to claim 41 [1] where the defined type is the given person and the first other person is a known person, such as a victim, the method involves the establishment of a probability value that the given person's allele identity or identities has not been detected.

17. (Amended) A method according to claim 41 [16] in which the probability value relates to the given person's allele identity being different from that of the known first other person's.

18. (Amended) A method according to claim 41 [16] in which the probability value relates to the given person's allele identity being the same as that of the known first other person's.

19. (Amended) A method according to claim 41 [1] in which the method further includes the prediction of the proportion of the mixture arising from the person other than the first other person, for instance from the suspect as the given person.

20. (Amended) A method according to claim 41 [1] in which the method includes an estimate or calculation of a value for p(null), the value for p(null) being calculated from a cumulative probability density function.

21. (New) A method for indicating the likelihood that a DNA mixture arose from sources of a defined type where the DNA mixture is formed by DNA samples from more than one source, the method involving:-

the determination of the identity of the single nucleotide polymorphism alleles present at a locus for the DNA in the mixture;

determining a first probability function for the situation where the mixture is formed from samples arising from the given person and from a first other person where the alleles identified have one or more of only two possible identities;

determining a second probability function for the situation where the DNA mixture is formed from samples arising from the second other person and a first other person where the alleles identified have one or both of only two possible identities;

using a first probability function as a numerator, and a second probability function as a denominator in determining a likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

determining such likelihood rations for a plurality of single nucleotide polymorphism loci; and

combining the likelihood ratios to give a combined likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

and where the minimum number of loci needed to achieve a minimum combined likelihood ratio is calculated from

$$\overline{LRn} = \prod_{m=1}^{mp} LR^{(fmxn)}$$

where n is the number of loci; mp is the number of possible allele identities for a sample mixture; LR is the likelihood; $\overline{LR}$ is the combined likelihood ratio; and fm is the frequency of occurrence of a particular mixture type m for a loci.

22. (New) A method according to claim 21 in which mp is 9.

23. (New) A method according to claim 21 in which the frequency of occurrence of a particular mixture type m for a loci is as stated in this claim in respect of the stated allele identities m:-

Mixture type (m)	AA,AA	AA,AB	AB,AA	AA,BB	BB,AA	AB,AB	AB,BB	BB,AB	BB,BB
Frequency (fm)	$\underline{fa^4}$	$\underline{f2a^3b}$	$\underline{2a^3b}$	$\underline{fa^2b^2}$	$\underline{fa^2fb^2}$	$\underline{4fa^2b^2}$	$\underline{2fafb^3}$	$\underline{2fafb^3}$	$\underline{fb^4}$

24. (New) A method according to claim 21 in which the minimum combined likelihood ratio is $1x10^4$ or more.

25. (New) A method according to claim 21 in which the minimum combined likelihood ratio is $1x10^{16}$ or more.

26. (New) A method according to claim 21 where the allele identity or identities of a given person and/or known first other person are under consideration, the method includes the determination of the allele identity or identities at one or more of the loci under consideration from DNA obtained only from the given person or known first person.

27. (New) A method according to claim 21 where the defined type is the given person and the first other person is a known person, such as a victim, and at least some of the loci considered in the method are those in which the given person and first other person are known to differ in allele identity.

28. (New) A method of estimating the minimum number of loci to be used in a method for indicating the likelihood that a DNA mixture arose from sources of a defined type where the DNA mixture is formed by DNA samples from more than one source, the method of estimating including selecting a minimum combined likelihood ratio and calculating the number of loci needed according to a theoretical likelihood ratio calculated from:

$$\overline{LRn} = \prod_{m=1}^{mp} LR^{(fmxn)}$$

where n is the number of loci; mp is the number of possible allele identities for a sample mixture; LR is the likelihood ratio; $\overline{LR}$ is the combined likelihood ratio; and fm is the frequency of occurrence of a particular mixture type m for a loci.

29. (New) A method according to claim 28 wherein mp is 9.

30. (New) A method according to claim 28 in which the frequency of occurrence of a particular mixture type m for a loci is as started in this claim in respect of the stated allele identities m:-

Mixture type (m)	AA,AA	AA,AB	AB,AA	AA,BB	BB,AA	AB,AB	AB,BB	BB,AB	BB,BB
Frequency (fm)	fn^4	$f2a^3b$	$2a^3b$	fa^2b^2	fa^2fb^2	$4fa^2b^2$	$2fafb^3$	$2fafb^3$	fb^4

31. (New) A method according to claim 28 in which the minimum combined likelihood ratio is $1x10^4$ or more.

32. (New) A method according to claim 28 in which the minimum combined likelihood ratio is $1x10^{16}$ or more.

33. (New) A method for indicating the likelihood that a DNA mixture arose from sources of a defined type where the DNA mixture is formed by DNA samples from more than one source the method involving:-

a determination of the identity of single nucleotide polymorphism alleles present at a locus in the DNA in the mixture;

determining a first probability function for a situation where the DNA mixture is formed from samples arising from a given person and from a first other person, where the alleles identified have one or both of only two possibilities;

determining a second probability function for a situation where the DNA mixture is formed from samples arising from a second other person and a first other person, where the alleles identified have one or both of only two possible identities;

using the first probability function as a numerator and the second probability function as a denominator in determining a likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

determining such likelihood ratios for a plurality of single nucleotide polymorphism loci; and

combining the likelihood ratios to give a combined likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

the method including the establishment of a probability value that a person's allele identity or identities have not been detected which reflects the probability that the identity or identities is present but is not distinguished from the background noise.

34. (New) A method according to claim 33 in which the probability value relates to the given person's allele identity being different from that of the known first other person's.

35. (New) A method according to claim 36 in which the probability is expressed as a likelihood ratio and the likelihood ratio, when the first allele A and a second allele B are suggested for the profile and second allele B is not detected, is defined according to the equation:-

$$LR = \frac{p(B \neq null)}{[2ab + b^2]p(B \neq null) + a^2 p(B = null)}$$

where a and b are allele frequencies of first allele A and second allele B respectively, =null relates to allele B not being present, and ≠null relates to allele B being present but not distinguished from the background noise.

36. (New) A method according to claim 33 in which the probability value relates to the given person's allele identity being the same as that of the known first other person's.

37. (New) A method according to claim 36 in which the probability value is expressed as a likelihood ratio and the likelihood ratio, when a first allele A and a second allele A are suggested for the profile, and allele B is not detected, is defined according to the equation:-

$$LR = \frac{p(B = null)}{[2ab + b^2]p(B \neq null) + a^2 p(B = null)}$$

where a and b are allele frequencies of A and B respectively, =null relates to allele B not being present, and ≠null relates to allele B being present but not distinguished from the background noise.

38. (New) A method according to claim 33 in which the method further includes the prediction of the proportion of the mixture arising from the person other than the first other person, for instance form the suspect as the given person.

39. (New) A method according to claim 33 in which the method includes an estimate or calculation of a value for p(null), the value for p(null) being calculated from a cumulative probability density function.

40. (New) A method according to claim 33 in which the probability value involves an investigation of the background noise level from the allele identity investigating process and / or the introduction of one or more negative control samples and / or the determination of a cumulative probability density function for one or more or all of the negative controls.

41. (New) A method for indicating the likelihood that a DNA mixture arose from sources of a defined type where the DNA mixture is formed by DNA samples from more than one source, the method involving:-

a determination of the identity of the single nucleotide polymorphism alleles present at a locus in the DNA in the mixture;

determining a first probability function for the situation where the DNA mixture is formed from samples arising from the given person and from a first other person, where the alleles identified have one or both of only two possibilities;

determining a second probability function for the situation where the DNA mixture is formed from samples arising from a second other person and a first other person, where the alleles identified have one or both of only two possible identities;

using the first probability function as a numerator and the second probability function as a denominator in determining a likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

determining such likelihood ratios for a plurality of singe nucleotide polymorphism loci; and

combining the likelihood ratios to give a combined likelihood ratio for the mixture having arisen from the defined type of sources considered in the first probability function;

where the defined type is the given person and the first other person is a known person, such as a victim, the method considers loci at which the given person and known first person are known to have the same homozygous allele identity and the method provides the establishment of a probability value that a person's allele identity or identities have not been detected which reflects the probability that the identity or identities is absent, rather than present but not detected.